Future Webinar Conferences

March 24, 2010  12-1pm ET
Symptom Assessment and Management
Steven Weisbord, MD

April 28, 2010  12-1pm ET
Incorporating Palliative Care into the Dialysis Unit
Michael Germain, MD

To register contact:
Samantha Dorr
Mid-Atlantic Renal Coalition
804.794.3757
sdorr@nw5.esrd.net
For additional information, including resources for patients and families, visit www.kidneyeol.org

- Advance care planning information
- Do not resuscitate orders in the dialysis unit
- Access to hospice
- Clinician educational resources

Contact the Kidney End of Life Coalition at kidneyeol@nw5.esrd.net
Pain Assessment and Management in ESRD

Sara Davison
Objectives

- Discuss the magnitude and impact of chronic pain in ESRD
- Discuss barriers to adequate pain assessment and management in ESRD
- Outline potential strategies to enhance pain assessment and management in ESRD
Symptom Burden in Dialysis Patients
n = 507

Davison, et al KI 2006;69:1621
### Severity of Pain: Brief Pain Inventory Scores

<table>
<thead>
<tr>
<th>Severity</th>
<th>Mild (0-3)</th>
<th>Moderate (4-5)</th>
<th>Severe (6-10)</th>
<th>Mean BPI Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst</td>
<td>17.5%</td>
<td><strong>82.5%</strong></td>
<td>27.2%</td>
<td>7.03</td>
</tr>
<tr>
<td>Least</td>
<td>74.8%</td>
<td>16.5%</td>
<td><strong>8.7%</strong></td>
<td>3.07</td>
</tr>
<tr>
<td>Average</td>
<td>41.7%</td>
<td><strong>58.3%</strong></td>
<td>27.2%</td>
<td>5.61</td>
</tr>
<tr>
<td>Now</td>
<td>44.7%</td>
<td>28.2%</td>
<td><strong>27.2%</strong></td>
<td>4.99</td>
</tr>
</tbody>
</table>

Cause of pain is NOT predictive for severity of pain

Davison, AJKD 2003
The Impact of Pain and Overall Symptom Burden for ESRD Patients

<table>
<thead>
<tr>
<th></th>
<th>No – Mild pain</th>
<th>Mod – Severe pain</th>
<th>Odds Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>18%</td>
<td>34%</td>
<td>2.31</td>
<td>0.01</td>
</tr>
<tr>
<td>Insomnia</td>
<td>53%</td>
<td>75%</td>
<td>2.32</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Davison JPSM 2005

Symptom burden accounted for 29% of the impairment in physical HRQL and 39% of the impairment in mental HRQL.

Davison KI 2006

Change in symptom burden accounted for 34% of the change in physical HRQL and 46% of the change in mental HRQL.

Davison NDT 2006
# Point Prevalence of Analgesic Use: DOPPS

Bailie GR et al, KI 2004

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>N = 2988</td>
</tr>
<tr>
<td>Any analgesic</td>
<td>30.2%</td>
</tr>
<tr>
<td>Any narcotic</td>
<td>18.0%</td>
</tr>
<tr>
<td>Any NSAID</td>
<td>6.4%</td>
</tr>
<tr>
<td>Any acetaminophen</td>
<td>11.1%</td>
</tr>
</tbody>
</table>

\(\frac{3}{4}\) of patients reporting moderate to severe pain were not prescribed analgesics
Complicated pharmacokinetics and pharmacodynamics

Uremic symptoms may mimic opioid toxicity

Treatment algorithms for cancer may not apply to ESRD

Elderly

Limb preservation

Pain is often experienced in the context of multiple, complex symptoms and EOL issues
  - Interfere markedly with psychological, social and physical coping skills

Lack of recognition of the problem

Therefore not a clinical or research focus – a unique body of knowledge is required to integrate nephrology & PC

Implementation of a standardized symptom screening & assessment process may improve provider recognition & treatment of symptoms
## Symptom Screening - ESAS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>0-10</td>
</tr>
<tr>
<td>Tired</td>
<td>0-10</td>
</tr>
<tr>
<td>Nausea</td>
<td>0-10</td>
</tr>
<tr>
<td>Depression</td>
<td>0-10</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0-10</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0-10</td>
</tr>
<tr>
<td>Appetite</td>
<td>0-10</td>
</tr>
<tr>
<td>Feeling of well-being</td>
<td>0-10</td>
</tr>
<tr>
<td>Itching</td>
<td>0-10</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>0-10</td>
</tr>
</tbody>
</table>

### Instructions
- Please circle the number that best describes each symptom.
- Complete by (check one):
  - Patient
  - Caregiver
  - Caregiver assisted

**BODY DIAGRAM ON REVERSE SIDE**
# Questionnaire POS-S1 - Patient

Below is a list of symptoms, which you may or may not have experienced. Please put a tick in the box to show how each of these symptoms has affected how you have been feeling over the last 3 days.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Not at all, no effect</th>
<th>Slightly but not bothered by it</th>
<th>Moderately — limits some activity or concentration</th>
<th>Severely — activities or concentration markedly affected</th>
<th>Overwhelmingly — unable to think of anything else</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness or lack of energy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea (feeling like you are going to be sick)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting (being sick)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor appetite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouth problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor mobility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restless legs or difficulty keeping legs still</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling anxious</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling depressed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Changes in skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Dialysis Symptom Index

**During the past week:** Did you experience this symptom?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Did you experience this symptom?</th>
<th>If &quot;yes&quot;: How much did it bother you?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not At All</td>
<td>A Little Bit</td>
</tr>
<tr>
<td>1. Constipation</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>2. Nausea</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>3. Vomiting</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>4. Diarrhea</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>5. Decreased appetite</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>6. Muscle cramps</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>7. Swelling in legs</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>8. Shortness of breath</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>9. Lightheadedness or dizziness</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>10. Restless legs or difficulty keeping legs still</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td><strong>During the past week:</strong> Did you experience this symptom?</td>
<td><strong>If “yes”: How much did it bother you?</strong></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not At All</td>
<td>A Little Bit</td>
</tr>
<tr>
<td>11. Numbness or tingling in feet</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES →</td>
<td>1</td>
</tr>
<tr>
<td>12. Feeling tired or lack of energy</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES →</td>
<td>1</td>
</tr>
<tr>
<td>13. Cough</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES →</td>
<td>1</td>
</tr>
<tr>
<td>14. Dry mouth</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES →</td>
<td>1</td>
</tr>
<tr>
<td>15. Bone or joint pain</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES →</td>
<td>1</td>
</tr>
<tr>
<td>16. Chest pain</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES →</td>
<td>1</td>
</tr>
<tr>
<td>17. Headache</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES →</td>
<td>1</td>
</tr>
<tr>
<td>18. Muscle soreness</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES →</td>
<td>1</td>
</tr>
<tr>
<td>19. Difficulty concentrating</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES →</td>
<td>1</td>
</tr>
<tr>
<td>20. Dry skin</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES →</td>
<td>1</td>
</tr>
<tr>
<td>21. Itching</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES →</td>
<td>1</td>
</tr>
<tr>
<td>22. Worrying</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES →</td>
<td>1</td>
</tr>
<tr>
<td>During the past week: Did you experience this symptom?</td>
<td>If “yes”: How much did it bother you?</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>--------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not At All</td>
<td>A Little Bit</td>
</tr>
<tr>
<td>23. Feeling nervous</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>24. Trouble falling asleep</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>25. Trouble staying asleep</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>26. Feeling irritable</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>27. Feeling sad</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>28. Feeling anxious</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>29. Decreased interest in sex</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>30. Difficulty becoming sexually aroused</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
</tbody>
</table>
Pain Assessment

- Pain history - Appropriate investigations and diagnosis
  - Onset
  - Location
  - Duration
  - Intensity
  - Severity – impact on HRQL
  - Temporal characteristics
  - Triggering/relieving factors
  - Type (nociceptive, neuropathic)
  - Psychological symptoms
  - Treatment (duration, dosage, side-effects)
  - Goals & expectations of treatment
<table>
<thead>
<tr>
<th>Etiology of Pain</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td>63.1</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>19.4</td>
</tr>
<tr>
<td>Musculoskeletal: Not yet diagnosed</td>
<td>18.4</td>
</tr>
<tr>
<td>Osteoporosis (resulting in spinal fractures)</td>
<td>9.7</td>
</tr>
<tr>
<td>Inflammatory Arthritis</td>
<td>6.8</td>
</tr>
<tr>
<td>Renal Osteodystrophy</td>
<td>4.9</td>
</tr>
<tr>
<td>Discitis/Osteomyelitis</td>
<td>1.9</td>
</tr>
<tr>
<td>Related to Dialysis Procedure</td>
<td>13.6</td>
</tr>
<tr>
<td>Peripheral Polyneuropathy</td>
<td>12.6</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>Other</strong> (including trauma, PCKD, malignancy, calciphylaxis)</td>
<td>20.3</td>
</tr>
</tbody>
</table>

Davison, AJKD 2003
Calciphylaxis (calcific uremic arteriolopathy)
**Osteitis Fibrosa**

Bone and joint pain on exertion in skeletal sites that are subject to biomechanical stress. Frequently associated with calcium phosphate deposition in arteries, joints, soft tissues, and the viscera; may be associated with proximal myopathy, ruptured tendons, pseudogout, and calciphylaxis.

**Adynamic Bone disease:** bone and joint pain (at rest and with exertion), fractures, skeletal deformities
Pain Assessment

- **Pain history**, appropriate investigations and diagnosis
- **Type of pain** (nociceptive, neuropathic, or both) directs analgesic strategy
  - DN4
**Questionnaire DN4**

Please complete this questionnaire by ticking one answer for each item in the 4 questions below.

### INTERVIEW OF THE PATIENT

**Question 1:** Does the pain have one or more of the following characteristics?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - Burning</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2 - Painful cold</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>3 - Electric shocks</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

**Question 2:** Is the pain associated with one or more of the following sensations in the same area?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 - Tingling</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>5 - Pins and Needles</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>6 - Numbness</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>7 - Ticking</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

### EXAMINATION OF THE PATIENT

**Question 3:** Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 - Touch Hypoesthesia</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>9 - Pricking Hypoesthesia</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

**Question 4:** In the painful area, can the pain be caused or increased by:

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 - Brushing</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
Pain Assessment

- **Pain history**, appropriate investigations and diagnosis
- **Type of pain** (nociceptive, neuropathic, or both) directs analgesic strategy

- **Regular assessment and recording** of pain severity, effects on functioning and HRQL, and adverse effects of current management
  - This can be largely **protocol driven**
  - Possible role for **advanced nurse practitioner**

- Pharmacologic and non-pharmacologic interventions
Principles of Pain Management

- ‘by mouth’
- ‘by the clock’
- ‘by the ladder’
- ‘for the individual’
- ‘attention to detail’
Freedom from pain

OPIOID FOR MODERATE TO SEVERE PAIN
± NON-OPIOID
± ADJUVANT

Pain persisting or increasing

WEAK OPIOID FOR MILD TO MODERATE PAIN
± NON-OPIOID
± ADJUVANT

Pain persisting or increasing

NON-OPIOID
± ADJUVANT

PAIN
Efficacy of the WHO Analgesic Ladder to Treat Pain in ESRD

45 HD patients

Initial Pain Score (0-10)
Post Treatment Pain Score (0-10)

Neuropathic Pain
Nociceptive Pain

Type of Pain

Barakzoy, JASN 2006
WHO Analgesic Ladder: Step 1

Acetaminophen

- Does not require dose adjustment in ESRD
- Non-narcotic of choice for mild-moderate pain in CKD/ESRD
WHO Analgesic Ladder: Step 1

**NSAIDS**
- Can be used in conjunction with acetaminophen
- Increased risk of bleeding with CKD/ESRD
- Potential cardiovascular risks associated with COX-2 inhibitors
- Renal side effects: hypertension, hyponatremia, loss of RRF, hyperkalemia
- Topical agents can be used effectively
- More appropriate for specific acute indications e.g. gout v. chronic use
WHO Analgesic Ladder: Step 2

Tramadol

- Non-opioids with similar side effects to opioids
- Should not be given to patients on SSRIs
- Prolongation of ½ life in renal failure (metabolized in liver with renal excretion of active metabolites).
- May be epileptogenic in conditions with lowered seizure threshold such as ESRD
- Maximum dose is 50mg BID
Opioids

- Active metabolites are renally excreted

Side Effects

- Constipation
- Nausea and vomiting
- Decreased appetite
- Pruritus
- Hypotension
- CNS and respiratory depression
WHO Analgesic Ladder: Step 2

Codeine

- Weak opioid

- Elimination ½ life is significantly increased in dialysis patients
  - Reports of neurotoxicity
  - Toxicity is unpredictable

- Should not be used
WHO Analgesic Ladder: Step 2

Dextropropoxyphene

- Weak opioid
- Usually prescribed in combination with acetaminophen
- Major active metabolite is norpropoxyphene:
  - Accumulates in CKD
  - Associated with toxicity
- Dextropropoxyphene is not recommended for use in patients with severe CKD
- It has been withdrawn from use in the UK.
WHO Analgesic Ladder: Step 3

Oxycodone

- Elimination significantly decreased in ESRD
  - Fibrillary GN
  - Growing popularity as a drug of abuse and is now considered one of the most desirable of prescription drugs

- Should be used with caution in ESRD
WHO Analgesic Ladder: Step 3

Morphine

- Active metabolite M6G is renally excreted and accumulates in ESRD: increased side effects and toxicity

- No data regarding dose adjustments for sustained-release preparations of morphine

- Should not be used for chronic pain management
WHO Analgesic Ladder: Step 3

Hydromorphone

- 5-7 times more potent than morphine (when administered orally), shorter duration of action

- Case reports of adverse effects

- Published and clinical experience indicates that it may be administered safely in ESRD
  
  - May be particularly useful in patients who have intolerable side effects from other narcotics
  - May cause less pruritus, sedation, & nausea

Lee MA, Palliat Med 2001
Non-Compartmental Pharmacokinetics for Hydromorphone and H3G (n=12)

<table>
<thead>
<tr>
<th>Phase</th>
<th>t1/2 (h)</th>
<th>AUC(Tau) (ng.h/mL)</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydromorphone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>3.2 ± 2.4</td>
<td>41.6 ± 20.3</td>
<td>1.8 ± 0.8</td>
</tr>
<tr>
<td>Multi-Dose</td>
<td>5.9 ± 4.4</td>
<td>33.9 ± 27.3</td>
<td>2.7 ± 1.6</td>
</tr>
<tr>
<td><strong>Hydromorphone-3-Glucuronide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>3.3 ± 2.1</td>
<td>3243.9 ± 2768.0</td>
<td>1.8 ± 0.7</td>
</tr>
<tr>
<td>Multi-Dose</td>
<td>33.3 ± 41.8</td>
<td>4229.9 ± 2975.4</td>
<td>12.5 ± 15.1</td>
</tr>
</tbody>
</table>

Davison, JOM 2008
Non-Compartmental Pharmacodynamics (n=12)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Maximum Analgesia (% ± SD)</th>
<th>Time to Max Analgesia (hours ± SD)</th>
<th>% time with analgesia (% ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis</td>
<td>-68.8 ± 37.5</td>
<td>1.8 (0.5 - 4.0)</td>
<td>-66.3 ± 40.1</td>
</tr>
<tr>
<td>Multi-dose</td>
<td>-65.5 ± 43.3</td>
<td>3.0 (0.5 - 4.0)</td>
<td>-40.2 ± 21.8</td>
</tr>
</tbody>
</table>

Davison, JOM 2008
Methadone

- Opioid commonly used for treatment of severe pain or withdrawal in opioid addicts

- High oral bioavailability and a long ½ life

- Essentially no PK data in ESRD; single report suggesting normal levels in ESRD
  - Excreted mainly in the feces, with metabolism into pharmacologically inactive metabolites primarily in the liver, although ~20% is excreted unchanged in the urine

- Anecdotal experience suggests a relatively good safety profile in ESRD if monitored carefully.
Fentanyl (transdermal formulation)

- When patients are on a stable narcotic dose
- Essentially no PK data of transdermal formulation or effect of dialysis on levels (one report stated poor removal)
- Toxicity has been reported but anecdotal experience suggests a reasonable safety profile in ESRD if monitored carefully
WHO Analgesic Ladder: Step 3

Buprenorphine
Semisynthetic opioid with a long duration of action
- 30 - 60 x as potent as oral morphine when given SL
- Metabolized by the liver, little unchanged drug in the urine
- The two major metabolites excreted in the urine
  - Buprenorphine-3-glucuronide (B3G): inactive
  - Norbuprenorphine: is a less potent analgesic
- Administered sublingually or via a transdermal patch.
- Given these properties and the minimal changes in kinetics in renal failure, it may be a potentially useful analgesic for use in CKD
  - Might be difficult to antagonize with opioid antagonists
  - Care should be taken when used with benzodiazepines
WHO Analgesic Ladder: Step 3

Pethidine (Meperidine)

- Active metabolite norpethidine accumulates in patients with renal impairment
  - neuroexcitatory effects and risk of convulsions

- DO NOT use in CKD
Adjuvants: Neuropathic Pain

Antidepressants

- Tricyclic antidepressants: synergistic with opioids

- Anticholinergic effects: dry mouth; sedation, weight gain; caution in patients with cardiac conduction abnormalities
  - minor adverse events occur in about one-third of patients
  - Despiramine may have less side effects than amitriptyline
  - Selective serotonin re-uptake inhibitors (SSRIs) appear to be less effective as adjuvant analgesics but have fewer adverse reactions
Adjuvants

Anticonvulsants

- **Gabapentin**: effective for neuropathic pain and restless legs
  - Suppresses depolarization of afferent pain neurons by inhibiting calcium influx
  - Accumulation with toxicity in ESRD – Max dose 300mg/day
  - **Pregabalin**: identical mechanism of action as gabapentin for the tx of neuropathic pain.

- **Carbamazepine**: neuropathic pain
  - Does not require dose adjustment in ESRD
  - Start @ 200mg BID
Clinical Algorithm & Preferred Medications to Treat Pain in Dialysis Patients

Developed by the Mid-Atlantic Renal Coalition and the Kidney End-of-Life Coalition

September 2009

This project was supported, in part, under CMS Contract #HHSM-500-2006-NW005C. The contents of this document do not necessarily reflect CMS policy.

OVERVIEW OF ESSENTIALS OF PAIN MANAGEMENT

- Assess pain intensity on a 0-10 scale in which 0 = no pain at all and 10 = the worst pain imaginable. Determine if the pain is mild (1-4), moderate (5-6), or severe (7-10).
- Prescribe pain medications and dosages according to the World Health Organization 3-Step Analgesic Ladder adapted for patients with chronic kidney disease (see page 2).
- Assess the character of the patient’s pain and determine whether it is nociceptive, neuropathic, or both. Patients may have more than one type of pain; each pain syndrome should be diagnosed and treated.
- Nociceptive pain involves intact pain receptors and is described by patients as aching, dull, throbbing, cramping, or pressure. Neuropathic pain involves injury to pain receptors and is described by patients as tingling, burning, stabbing, or numb (see pages 3 & 4). Treatment of severe neuropathic pain usually requires opioid medications in addition to gabapentin or pregabalin, or other medications specific for neuropathic pain.
- Assess pain regularly for site, relieving and aggravating factors, and temporal relationships, and assess treatment regularly for effect on functioning and quality of life.
- Believe the patient’s report of pain.
- Refer for nonpharmacological interventions as appropriate.
- Use adjuvant medications to reduce pain and side effects.
- Anticipate and treat constipation.
- Always consider depression as a potential contributor.
- Screen for opioid abuse.

RECOMMENDED PRACTICES

A Educate patient/caregivers on pain assessment and charting at home, goals of therapy, management plan, and potential complications.

B Aim to achieve control at a level acceptable to the patient; it may not be necessary or possible to make the patient completely pain-free. Provide pm doses for breakthrough pain.

C For chronic pain, schedule doses over 24 hours on a regular basis. Additional “breakthrough” medication should be available on an “as needed” basis.
**Analgesic Ladder**

**WHO 3-Step Analgesic Ladder**

**Severe Pain (7-10)**
- Hydromorphone - start at 1 mg PO q 4h + 1 mg prn for breakthrough pain q 2h

**Moderate Pain (5-6)**
- Hydrocodone - start at 5 mg po q 4h prn
- Oxycodone - start at 5 mg po q 4h prn
- Tramadol - start at 25 mg po q d
- ± Nonopioid analgesics ± Adjuncts

**Mild Pain (1-4)**
- Acetaminophen
  - Avoid NSAIDS
  - ± Adjuncts

*Do not exceed 4 g of the acetaminophen per day to avoid hepatotoxicity.*

**Adjuncts** include medications such as anticonvulsants for neuropathic pain. It may also refer to medications that are administered to manage an adverse effect of an opioid, or to enhance analgesia, such as steroids for pain from bone metastases.
Algorithm to Treat Severe Chronic Pain in Dialysis Patients

Hydromorphone:
- Start at 0.5 mg PO q 4 hours plus 1 mg PO q 2 hours prn pain. Titrate dosage every 2–3 days.
- If pain is not controlled, is continuous, and 24-hour dose exceeds 12 mg, substitute transdermal fentanyl 25 mcg/h for regular dose of hydromorphone.
- If further “as needed” hydromorphone exceeds 12 mg/24 hours, increase dose of fentanyl patch by further 25 mcg. Titrate upwards in similar manner if pain is not controlled.
- Caution: Toxic metabolite, H3G, accumulates if dialysis is stopped.

Fentanyl Transdermal Patches:
- Useful for patients with chronic, stable pain. Start after immediate-release opioid dose is established. Analgesia may not be obtained for 12-24 hours, so continue previous prn analgesics for 12 hours to ensure a smooth transition.
- Initial dose for opioid-naïve patients is 12 mcg/h (increase dose every 3–6 days as needed for pain). Useful choice if dialysis non-adherence or stopping dialysis are concerns.
- Fentanyl patches above 12 mcg/hr should not be used in opioid-naïve patients due to risk of respiratory depression.
- Prescribe medication for breakthrough pain.

Methadone:
- Only recommended to be used by knowledgeable physicians.
- Use if unable to control pain with hydromorphone or fentanyl (opioid-allergy, adverse effects, or refractory pain).
- Obtain baseline QTc (methadone may prolong QT interval) and repeat EKG if daily dose > 100 mg. QTc < 450 ms considered safe.
- Beware of multiple drug interactions and adjust dose.
- Consult www.hopweb.org for opioid conversions from hydromorphone or fentanyl to methadone.
**NOCICEPTIVE PAIN TREATMENT**

*Note: Monitor for opioid toxicity (sedation, hallucinations, myoclonus and/or asterixis) and opioid adverse effects (constipation, nausea and vomiting).*

- Confirm patient is able to swallow oral medications.
- Long-acting opioids should be started after the needed dosage to control pain is established with short-acting opioids.
- A rescue dose equivalent to 10% of the 24-hour dose of opioid should be available to be taken every 1-2 hours prn for breakthrough pain. Remember to recalculate the rescue dose when increasing the base dose (long-acting dose).
- If the patient is experiencing pain when he/she takes the long-acting opioid, he/she should take a rescue dose at the same time and not expect the long-acting opioid to relieve the breakthrough pain.

**NEUROPATHIC PAIN TREATMENT**

*Gabapentin:*
- Start 100 mg po q hs and increase weekly by 100 mg per night to a maximum of 300 mg q hs. Occasionally doses up to 600 mg a day can be safely used.
- If ineffective at maximum tolerated dose, discontinue and start Pregabalin.

*Pregabalin:*
- 25 mg q hs and increase every few days to 100 mg a day.
- If pain control is inadequate at target dose for 2 to 4 weeks, or intolerable adverse effects, discontinue and start Desipramine.

*Desipramine:*
- 10 mg po q hs. Titrate to adequate pain control or maximum dose of 150 mg q hs.
- If pain control still remains inadequate, institute WHO 3-Step Analgesic Ladder (see page 3).
MANAGEMENT OF OPIOID ADVERSE EFFECTS

Acute:
Excessive sedation, compromised respiration with low O₂ saturation
• Dilute 0.4 mg of Naloxone in 10 ml NS and administer 1 ml IV q 1-2 minutes until patient arouses.
• Continue to monitor for return of sedation or slowed respirations (half-life of Naloxone is shorter than half-life of opioids).

Chronic:
Nausea and/or vomiting
• Prochlorperazine 2.5 to 10 mg PO, SC or PR QID prn.
• Haloperidol 0.5 to 1 mg PO, SL, SC, IV BID-TID prn
  (Haloperidol solution is flavorless).
• Metoclopramide 5 to 10 mg PO, SC, IV QID prn.
• Dimenhydrinate may be used 2.5 to 50 mg PO, SC, IV but is less effective, except if secondary to motion/dizziness. It also reduces opioid-induced pruritus.
• Ondansetron 4-8 mg PO or IV q8H prn.

Constipation
• Start docusate sodium and stimulant laxative (e.g. Senna, Bisacodyl) at same time as opioids as preventative therapy.
• Lactulose at 15-30 ml po daily to BID is more effective for opioid-induced constipation but patients may prefer medication in pill form.

Cognitive impairment
• Try decreasing the opioid dose to determine if function improves. If it does, consider using a lower dose or a different pain medication.

References for this document can be found on the Kidney End-of-Life Coalition website: www.kidneyeol.org.
# Preferred Medications in CKD

## Recommended

- Fentanyl
- Methadone
- Hydromorphone
- Acetaminophen
- Gabapentin
  
  Doses up to 300 mg/d are generally considered safe in ESRD, but doses up to 600 mg should be used with caution; note that gabapentin use for neuropathic pain is off-label but effectiveness has been documented.

- Pregabalin
  
  Doses up to 100 mg/d are generally considered safe in ESRD.

## Use with Caution

- Tramadol
  
  Limit dose to 50 mg BiD. Higher doses have been used but caution needs to be taken since pharmacokinetics are not well established.

- Hydrocodone/Oxycodone
  
  Insufficient pharmacokinetic evidence to establish safety in CKD, but literature reports use without major adverse effects.

- Desipramine/Nortriptyline
  
  Alternative to treat neuropathic pain, but more adverse effects than gabapentin and pregabalin.

## Do Not Use

- Morphine
- Codeine
- Meperidine
- Propoxyphene

Morphine, codeine, meperidine, propoxyphene: Renally excreted metabolites accumulate in CKD causing neurotoxicity.
PAIN ASSESSMENT

Instructions: Please have your patient describe his/her level of pain by circling the appropriate number or the face that best describes the intensity of pain. Determine if the pain is nociceptive or neuropathic by the descriptors the patient uses to describe the pain (see algorithm below). Repeat the pain assessment on subsequent patient visits.

1. “Are you having any pain?”
   *Verbal:* “How much pain are you having, from 0 (no pain) to 10 (worst pain imaginable)?”
   *Written:* “Circle the number that describes how much pain you are having.”

**NUMERICAL RATING SCALE**

<table>
<thead>
<tr>
<th>No pain</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Worst imaginable pain</th>
</tr>
</thead>
</table>

**CATEGORICAL SCALE/FACES R**

- None (0)
- Mild (1-4)
- Moderate (5-6)
- Severe (7-10)

2. “Where is the pain located?”
   Record, screen and address each site.

3. “How much pain are you having?”
   *Use Pain Screening Tool—Numerical Scare or Categorical Faces/R Scale (for cognitively impaired).*

4. “What is the character of the pain?”
   - Nociceptive—Patient descriptors: aching, dull, throbbing, cramping, pressure
   - Neuropathic—Patient descriptors: tingling, numbness, burning, stabbing, increased pain to light touch
   - Both Nociceptive and Neuropathic

5. “What relieves the pain?”, “What aggravates the pain?”
Historical Use of Marijuana (Cannabis)

- Oldest known Neolithic culture in China
- An 1848 commentary in the British Pharmacopoeia outlined psychotropic, antispasmodic and analgesic effects of Cannabis
Marijuana (Cannabis)

- Marijuana is a crude drug obtained from the *Cannabis sativa* plant

- Consists of approximately 460 active components

- > 60 of these have the 21-carbon structure of typical cannabinoids
  - Δ9-THC$_1$
  - Analgesic, muscle relaxant, antiemetic, appetite stimulant, psychoactive effects
Cannabinoid Receptors

**CB₁ receptor**
- Found in the brain, spinal cord and peripheral nervous system.
  - Also present in various peripheral tissues such as heart and vasculature

**CB₂ receptor**
- Found on immune cells in peripheral tissues
  - More recently, found in the CNS

(Davison JS et.al. Science 2006)
Endogenous Cannabinoids

- **Anandamide (AEA):** 1992 “internal bliss”
  - endogenous ligand of the CB₁ receptor
  - resembles THC structurally: similar actions
  - levels in the brain ~ to neurotransmitters such as dopamine and serotonin.

- **2-arachidonyl glycerol (2-AG):**
  - Brain tissue concentrations ~ 200-fold higher than AEA
  - ~ 20 x higher than GABA
Putative Mechanism of Action of Endocannabinoids

Christie and Vaughan, 2001
Cannabinoid Drugs Approved by FDA and Health Canada

- **Dronabinol**: synthetic THC (Marinol)
  - Anorexia/wasting in patients with HIV
  - Emesis due to cancer chemotherapy

- **Nabilone**: synthetic cannabinoid similar to THC (Cesamet)

- **THC:CBD** Cannabis extract (Sativex)
  - Adjunctive tx for neuropathic pain (MS)
  - Adjunctive tx for cancer pain
Cannabidiol (CBD)

- Anti-inflammatory
- Antioxidant
- Anti-seizure
- Anxiolytic
- Antipsychotic properties.
- Inflammatory and neuropathic pain
## Cannabinoids v. Opioids

<table>
<thead>
<tr>
<th></th>
<th>Opioids</th>
<th>Cannabinoids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nausea &amp; Vomiting</strong></td>
<td>Increases</td>
<td>Decreases</td>
</tr>
<tr>
<td><strong>Appetite</strong></td>
<td>Decreases</td>
<td>Increases</td>
</tr>
<tr>
<td><strong>Agitation</strong></td>
<td>Increases</td>
<td>Decreases</td>
</tr>
<tr>
<td><strong>Sleep</strong></td>
<td>Disturbs</td>
<td>Improves</td>
</tr>
<tr>
<td><strong>Pruritus</strong></td>
<td>Increases</td>
<td>Decreases</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Sense of well-being</strong></td>
<td>+/-</td>
<td>Increases</td>
</tr>
<tr>
<td><strong>Psychosis/abuse</strong></td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>
Conclusions

- Chronic pain is common in ESRD and is typically severe
- Chronic pain has a substantial negative impact on HRQL
- Pain assessment tools for ESRD are available (mESAS)
- Pain algorithms for ESRD are available
Questions?
For questions about pain management, e-mail Samantha Dorr at sdorr@nw5.esrd.net and for information about pain management resources visit www.kidneyeol.org/ and click on Professional Resources

Contact the Kidney End of Life Coalition at kidneyeol@nw5.esrd.net
To Register for the Webinar Conferences on March 24 and April 28

Contact

Samantha Dorr
Mid-Atlantic Renal Coalition
804.794.3757
sdorr@nw5.esrd.net